TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	US APPLICATION NO. (If known, see 37 CFR 1.5)
P67002US0	09/890353

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/RU99/00463	1 December 1999	30 November 1999

TITLE OF INVENTION

INSULIN-CONTAINING MEDICAMENT FOR PERORAL APPLICATION AND METHOD FOR THE PRODUCTION THEREOF

APPLICANT(S) FOR DO/EO/US

Svetlana Alexandrovna MORENKOVA

Applicant herein submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for Internatl. Preliminary Examination was made by the 19th month from earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the Internatl. Preliminary Examination report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    International Search Report – Russian Patent Office
    First Page of Publication

JC17 Rec'd PCT/PTO 30 JUL 2001

US APPLICATION NO.(If known, see 37 CFR 1 5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/890353	PCT/RU99/00463	P67002US0

	CALCULATIONS	PTO USE ONLY
17. ☒ The following fees are submitted:		
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Internatl. prelim. examination fee paid to USPTO (37 CFR 1.492 (a) (1)) .. $690.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (2)) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) .. $710.00		
Neither international preliminary examination fee (37 CFR 1.492 (a) (3)) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO) **$1000.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (4)) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
Search Report prepared by the EPO or JPO (37 CFR 1.492 (a) (5)) **$860.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 1000.00	
Surcharge of $130.00 for furnishing the **oath or declaration** later than ☐ **20** ☐ **30** months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	**Number Filed**	**Number Extra**	Rate		
Total Claims	**12** - 20 =	-0-	x $18.00	$	
Independent Claims	**2** - 3 =	-0-	x $80.00	$	
Multiple Dependent Claim(s) (if applicable)			+ $270.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 1000.00	
Reduction by 1/2 for filing by **small entity**, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$ 500.00	
SUBTOTAL =				$ 500.00	
Processing fee of $130 for furnishing the **English translation** later than ☐ **20** ☐ **30** months from the earliest claimed priority date (37 CFR 1.492(f))				$	
TOTAL NATIONAL FEE =				$ 500.00	
Fee of $40.00 for recording the enclosed **assignment** (37 CFR 1.21(h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31).				$ 40.00	
TOTAL FEES ENCLOSED =				$ 540.00	
				Amt. to be refunded:	$
				Amt. charged:	$

a. ☒ A check in the amount of $ 540.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. **06-1358** in the amount of $ ____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge my account any additional fees set forth in §1.492 during the pendency of this application, or credit any overpayment to Deposit Account No. **06-1358**. A duplicate copy of this sheet is enclosed.

SEND ALL CORRESPONDENCE TO:

JACOBSON HOLMAN PLLC
400 7th Street, N.W., Suite 600
Washington, DC 20004
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By _____
John C. Holman
Reg. No. 22,769

JPH&S 3/95

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Svetlana A. MORENKOVA

Serial No.: New

Filing Date: July 30, 2001

For: INSULIN-CONTAINING MEDICAMENT FOR PERORAL APPLICATION AND METHOD FOR THE PRODUCTION THEREOF

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS

Please amend claims 3-6 and 10-12 as follows:

3. (Amended) Medicine on claim 1, characterized in the fact that the content of auxiliary substance makes 1-2,5 mass%.

4. (Amended) Medicine on claim 1, characterized in the fact that erythrocytes excreted from fresh pig, livestock or horse blood can be used as erythrocytes.

5. (Amended) Medicine on claim 1, characterized in the fact that it contains erythrocytes excreted from fresh human blood.

6. (Amended) Medicine on claim 1, characterized in the fact that it contains glutarite dialdehyde.

10. (Amended) Method on claim 7, characterized in the fact that erythrocytes excreted from fresh pig, livestock or horse blood are used as erythrocytes.

11. (Amended) Method on claim 7, characterized in the fact that it contains erythrocytes excreted from fresh human blood.

12. (Amended) Method on claim 7, characterized in the fact that it contains glutarite dialdehyde as a stitching agent.

REMARKS

The foregoing Preliminary Amendment is requested in order to delete the multiple dependent claims and avoid paying the multiple dependent claims fee.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Early action on the merits is respectfully requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By _____

John C. Holman
Reg. No. 22,769

400 Seventh Street, N.W.
Washington, D.C. 20004-2201
(202) 638-6666

Atty. Docket: P67002US0
Date: July 30, 2001
JCH:jrc

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

3. (Amended) Medicine on claim 1 ~~any of the items 1 or 2~~, characterized in the fact that the content of auxiliary substance makes 1-2,5 mass%.

4. (Amended) Medicine on claim 1 ~~any of the items 1-3~~, characterized in the fact that erythrocytes excreted from fresh pig, livestock or horse blood can be used as erythrocytes.

5. (Amended) Medicine on claim 1 ~~any of the items 1-3~~, characterized in the fact that it contains erythrocytes excreted from fresh human blood.

6. (Amended) Medicine on claim 1 ~~any of the items 1-5~~, characterized in the fact that it contains glutarite dialdehyde.

10. (Amended) Method on claim 7 ~~any of the items 7-9~~, characterized in the fact that erythrocytes excreted from fresh pig, livestock or horse blood are used as erythrocytes.

11. (Amended) Method on claim 7 ~~any of the items 7-9~~, characterized in the fact that it contains erythrocytes excreted from fresh human blood.

12. (Amended) Method on claim 7 ~~any of the items 7-11~~, characterized in the fact that it contains glutarite dialdehyde as a stitching agent.

Law Offices of

JACOBSON, PRICE, HOLMAN & STERN, PLLC

THE JENIFER BUILDING

400 SEVENTH STREET, N.W.

WASHINGTON, D.C. 20004

Atty's Docket No. _____

SMALL ENTITY DECLARATION
[37 CFR 1.9(c-f)]

Each undersigned declares that:

(1) ☒ the application attached hereto.

(2) ☐ U.S. Application Serial No. _____, filed _____

(3) ☐ U.S. Patent No. _____ issued _____
is entitled to the benefits of "small entity" status for paying reduced fees under 35 USC 41(a) and (b) to the Patent and Trademark Office by virtue of the following:

(4) ☒ Each undersigned declares that he/she qualifies as an independent inventor, or would qualify had he/she made the invention, as defined in 37 CFR 1.9(c).

(5) ☐ The undersigned declares that he/she is an official empowered to act on behalf of the concern identified below; that this concern qualifies as a small business concern as defined in 37 CFR 1.9(d); that exclusive rights to the invention have been conveyed to and remain with the small business concern, or if the rights are not exclusive, that all other rights belong to small entities as defined in 37 CFR 1.9.

(6) ☐ The undersigned declares that he/she is an official empowered to act on behalf of the organization identified below; that this organization qualifies as a nonprofit organization as defined in

(a) ☐ 37 CFR 1.9(e)(1)

(b) ☐ 37 CFR 1.9(e)(2)

(c) ☐ 37 CFR 1.9(e)(3)

(d) ☐ 37 CFR 1.9(e)(4) State law of _____
that exclusive rights to the invention have been conveyed to and remain with the organization, or if the rights are not exclusive, that all other rights belong to organizations as defined in 37 CFR 1.9.

(7) Each person, concern or organization to which I/we have assigned, granted, conveyed or licensed, or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

(a) ☐ no such person, concern or organization

(b) ☒ persons, concerns or organizations listed below
[a separate declaration is required from each named person, concern or organization having rights to this invention averring to their status as "small entities."]

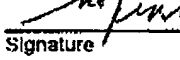
Full Name OTKRYTOE AKTSIONERNOE OBSCHESTVO "QUANTUM SATIS"

Address Samarinskaya,ul., d. 1/5 Mosoow 113191

☐ Individual ☒ Small Business Concern ☐ Nonprofit Organization

I/we acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement of small entity prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I/we hereby declare that all statements made herein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that those statements were made with the knowledge that willful false statements so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application, any patent issued thereon, or any patent to which this declaration is directed.

(8) MORENKOVA Svetlana Alexandrovna Typed Name of Inventor	 Signature	26.07.2001 Date
Typed Name of Inventor	Signature	Date
Typed Name of Inventor	Signature	Date
Typed Name of Inventor	Signature	Date

(9) _____
Name of Small Business Concern or Nonprofit Organization

Typed Name	By Signature	Date

Title of Signatory

Law Offices of

JACOBSON, PRICE, HOLMAN & STERN, PLLC

THE JENIFER BUILDING

400 SEVENTH STREET, N.W.

WASHINGTON, D.C. 20004

Attny's Docket No. _____

SMALL ENTITY DECLARATION
[37 CFR 1.9(c-f)]

Each undersigned declares that:

(1) ☒ the application attached hereto.

(2) ☐ U.S. Application Serial No. _____, filed _____

(3) ☐ U.S. Patent No. _____ issued _____

is entitled to the benefits of "small entity" status for paying reduced fees under 35 USC 41(a) and (b) to the Patent and Trademark Office by virtue of the following:

(4) ☐ Each undersigned declares that he/she qualifies as an independent inventor, or would qualify had he/she made the invention, as defined in 37 CFR 1.9(c).

(5) ☒ The undersigned declares that he/she is an official empowered to act on behalf of the concern identified below; that this concern qualifies as a small business concern as defined in 37 CFR 1.9(d); that exclusive rights to the invention have been conveyed to and remain with the small business concern, or if the rights are not exclusive, that all other rights belong to small entities as defined in 37 CFR 1.9.

(6) ☐ The undersigned declares that he/she is an official empowered to act on behalf of the organization identified below; that this organization qualifies as a nonprofit organization as defined in

(a) ☐ 37 CFR 1.9(e)(1)

(b) ☐ 37 CFR 1.9(e)(2)

(c) ☐ 37 CFR 1.9(e)(3)

(d) ☐ 37 CFR 1.9(e)(4) State law of _____;

that exclusive rights to the invention have been conveyed to and remain with the organization, or if the rights are not exclusive, that all other rights belong to organizations as defined in 37 CFR 1.9.

(7) Each person, concern or organization to which I/we have assigned, granted, conveyed or licensed, or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

(a) ☒ no such person, concern or organization

(b) ☐ persons, concerns or organizations listed below

[a separate declaration is required from each named person, concern or organization having rights to this invention averring to their status as "small entities."]

Full Name _____

Address _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

I/we acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement of small entity prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I/we hereby declare that all statements made herein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application, any patent issued thereon, or any patent to which this declaration is directed.

(8)

Typed Name of Inventor	Signature	Date
Typed Name of Inventor	Signature	Date
Typed Name of Inventor	Signature	Date
Typed Name of Inventor	Signature	Date

(9) OTKRYTOE AKTSIONERNOE OBSCHESTVO "QUANTUM SATIS"

Name of Small Business Concern or Nonprofit Organization

Typed Name Borisov Alexandr	By _____ Signature	26.04.2001 Date

Title of Signatory Director

INSULIN-CONTAINING MEDICAMENT FOR PERORAL APPLICATION AND METHOD FOR THE PRODUCTION THEREOF

The invention refers to medical science and deals with insulin-containing medicine for peroral use and its derivation method.

PRECEDING LEVEL OF TECHNIQUE

Diabetes – is one of the most widespread severe diseases, the absolute or relative deficiency of pancreas hormone, insulin, of which underlies it.

Insulin is a half-peptide hormone with molecular mass 6000. It impacts all types of metabolism in any organism: increases the penetration of glucose into organism tissues, prompts its utilization, reduces content of glycogen in liver and increases its number in muscles, enhances the intensity of protein synthesis and slows decomposition of the latter.

The principal method for injection of insulin into a human organism is hypodermic and intramuscular injection of medication. The attempts of insulin injection in the most physiological and patient-suitable peroral way turned out to be unsuccessful, for insulin easily degrades under the influence of digestive ferments, the fact that leads to loss of its biological activity.

The main obstacle, occurred when creating peroral forms of insulin, is its low resistance to the behavior of proteolitic ferments of gastrointestinal tract.

Over the last decade there were numerous attempts to create peroral forms of insulin, nevertheless, so far it was impossible to create the efficiently acting medicine, able to compete in terms of its active properties with insulin injected.

The medicine of insulin for peroral use, which represents a water-oily micro-emulsion consisting of insulin, lipids and protease deterrent, is well known. Micro-

emulsion is then covered with carboxymethylcellulos (Cho Y.W., Flynn M., Lancet, 1989, #30, p.1518 Saffran M., Kurnar G.S.).

The substantial deficiency of this medicine along with the labor-intensive and expensive technology of manufacturing, is the carrier – carboxymethylcellulos which is subject to influence of micro-organism as well as able to absorb a great number of insulin, as the result of which the form derived doesn't correspond with the requirements of the efficient peroral use of insulin.

There is a widespread notion about insulin-containing medicine consisting of the core with the content of insulin and auxiliary substances and capsule made of biodegrading medium polymer (Savarlar C., et al., A new approach to the oral administration of insulin and other peptide drugs, Science, 1986, v.233, pp.1081-1084).

The medicine is produced by injection of 1-40 mg of crystal insulin and 200 mg of stoichiometric impurity of 5-methoxisalicylic acid and sodium bicarbonate. Then the capsule (tablet) is covered with so-polymer of hydroxiethylmethacrylate and styrene, stitched with devinylazobenzene. The capsule is resistant to the effect of stomach medium and thin intestines, but gets decomposed in thick intestines under the influence of microorganisms existing there.

The deficiency of this medium is its low efficiency and undefined time for reaching maximum effect. Peroral injection of the said medicine, containing 1 unit of insulin, into rats leads to reduction of glucose concentration in blood by 20% within 9 hours after the injection. At the same time the intramuscular injection of insulin solution in the dose 0,1 or 1,0 units causes the reduction in the level of glucose in blood by 39 and 63% respectively. The maximum hypoglycemic effect for certain animals is reached within the period from 1 to 9 hours, and for some animals the effect of reduction in glucose concentration is missing even in 10 hours after the injection of medicine.

A solid insulin-containing medicine, consisting of the core containing inhibitor of proteolitic ferments and auxiliary substances and stomach-resistant capsule (Ehud Ziv, Miriam Kidron, Itamar Raz et al., Oral administration of insulin of solid form to non-diabetic and diabetic dogs. Journal of Pharmaceutical Science 1994, x.83, #6, pp.792-794 and Kidron M., Krausz M., Raz I et al., The absorption of Insulin: from the intestine in dogs, Nenside. Surfactants. Deterg. 1989, v.26, #5, pp.352-354) is well known.

The medicine contains the inhibitor of trypsin made of soy as the inhibitor of proteolitic ferments and sodium cholate and lactose – as auxiliary substances. Lactose is used as a non-active filler, and sodium cholate as a compound enabling to enhance the penetration of insulin through intestines walls.

The deficiency of this medicine is its low efficiency. Thus, when the medicine is injected in a peroral way into healthy dogs with the insulin dose 40 units/kg. of animal's weight, the maximum reduction in glucose concentration in animal's blood makes 18%, though with a hypodermic injection the similar hypoglycemic effect may be reached with the insulin dose 10 times lower. Besides, the abovementioned medicine containing the inhibitor of trypsin made of soy has a selective effect towards various types of animals, in other words, it is not a universal one. Thus, when used in a peroral way it reveals activity towards dogs and reveals no activity towards rats (Kidron M., Krausz M., Raz I et al., The absorption of Insulin: from the intestine in dogs, Nenside. Surfactants. Deterg. 1989, v.26, #5, pp.352-354).

An insulin-containing medicine, intended to treat patients with diabetes in a peroral way, which consists of the core sampling containing insulin, albuminous inhibitor of proteolitic ferments and represents a stitched hydrophilic polymer, modified by ovomukoide, and auxiliary substances and stomach-resistant capsule (Ru Nr.2117488 C1, 20.08.98), is well known.

The medicine contains 10 UNITS of insulin per one tablet. The medicine ensures a statically trustworthy hypoglycemic effect on various types of mammals, including the human being, meaning it has a universal nature.

Moreover, doses required to reach the necessary therapeutic effect are comparable with the levels for injection insulin. But the said medicine possesses low resistant properties, the term of experiment – up to 50 days as well as a comparatively low specific activity 20EA per 1g of dry tablet.

The method for derivation of insulin-containing polymer hydro-gels, including immobilization of insulin in the volume of stitched polymer, modified by inhibitor of proteolitic ferments – ovomukoides (Ru Nr.2066551 C1, 20.09.96).

The method enables to derive medicine, possessing activity, which makes 60-70% of the activity of insulin medicine during hypodermic injection. But the content of insulin in 1g of hydro-gel is not high.

The closest to the invention proposed is the method for derivation of medicine for peroral use, including insulin incubation with erythrocytes in proportion 1-4:100 in the presence of stitching agent in final concentration 0.15-0.25% (Ru Nr.2058788 C1, 20.04.96).

Consequently, medicine with the content 1000 E/1g of dry mass has been derived with the storage period in lyophilized state – up to several years.

DISCLOSURE OF INVENTION

The task of the invention proposed is to create an insulin-containing medicine for peroral use, meaning resistant to the effect of proteolitic ferments in gastrointestinal tract with the increased insulin content in 1g of dry substance, the fact that expands the potential for using the medicine in various medical forms.

The essence of the invention is as follows: insulin-containing medicine for peroral use represents insulin, immobilized on erythrocytes of fresh mammal blood in the presence of stitching agent in proportion %: insulin: erythrocytes of fresh mammal blood 5-10: 100 and auxiliary substance with the insulin content in lyophilized state 1250-2000 E of insulin per 1g of dry mass.

The said medicine as an auxiliary substance may contain gelatin in the amount from 1 to 2,5%.

The said medicine includes erythrocytes excreted from the fresh pig, horse or human blood as erythrocytes during insulin immobilization.

The said medicine may contain glutarite dialdehyde as a stitching agent.

The method for derivation of insulin-containing medicine for peroral use includes the excretion of erythrocytes from fresh mammal blood, their incubation with insulin in proportion mass %: insulin: erythrocytes from fresh mammal blood 5-10: 100 in final content of stitching agent 0,05-0,35% within 4-6 hours under the temperature 4-8° C, along with this, in the process of excretion of erythrocytes the blood is influenced by centrifugal forces with the size 350-1100*g within 15-30 minutes, and when insulin is incubated with erythrocytes, pendular rocking of composition with the frequency 0.1-0.5 Hz occurs, moreover, washing of the immobilized insulin is performed in several cycles, given the effect of centrifugal forces in each cycle with the size 350-1100* g within 0.5-10 minutes.

The above stated immobilization conditions enable to increase insulin content in the immobilized product up to 1250-2000 E of insulin in 1g of dry substance.

The technical outcome of the invention boils down to the fact that in maintaining stable hypoglycemic effect the activity and preservation qualities of the medical form derived is enhanced not only in a lyophilized but in a liquid state too.

The invention is implemented in the following way:

Example 1: erythrocytes were excreted from the fresh blood adding 1/10 volume of 3.8% sodium citrate during the effect of centrifugal forces 400*g within 30 minutes under the temperature 4°C. Erythrocytes were washed twice with four-fold volume 0.15M of sodium chloride solution. 20ml of erythrocytes dredge were added by 10ml of 0.1M of phosphate buffer solution pH 6.8 containing 0.15M of sodium chloride, 50ml of 1% crystal insulin solution and 1% of glutarite dialdehyde solution up to final concentration in the solution 0.05% and incubated the composition during pendular rocking with the frequency 0,5 Hz under the temperature 6°C within 6 hours, proportion insulin: erythrocytes 5:100. Then the suspension was washed from the non-mixed up insulin and glutarite dialdehyde ten times with ten-fold volumes 0.15M of sodium chloride solution during the effect of centrifugal forces with the size 1100* g within 5 minutes. After the last washing the sediment was added by gelatin solution as a stabilizer up to final concentration 2.5%, stirred thoroughly for 10 minutes under the room temperature and dried in a lyophilized way.

Derived 2 g of ready product representing powder of brownish color with the content 1250 E of insulin on 1g of dry product.

Example 2: derivation of insulin-containing medicine as in the example 1, except for the fact that 100mg of 1% crystal insulin solution and afterwards glutarite dialdehyde was added up to final concentration 0.35% proportion insulin: erythrocytes 10:100. The composition was incubated for 4 hours. Prior to lyophilization gelatin was added up to final concentration 1%.

Derived ready product with insulin content 2000 E on 1g of dry product. Proportion insulin: erythrocytes 10:100. Prior to use the medicine was emulged in the water up to required concentration.

Example 3: Testing of insulin-containing medicine was conducted on rats with experimental diabetes, caused by streptozotocine. Streptozotocine was injected intraperitoneally into male rats as taken 120mg/kg of animal mass. Streptozotocine was dissolved in citrate buffer pH 4,5 directly prior to injection. In 48 hours insulin-containing medicine, immobilized with the help of glutarite dialdehyde as taken 15-20 units of insulin in medicine (per one animal), prepared as in the example, was injected through probe into animals and in three hours glucose content was determined in the animal blood. Animals with streptozotocine diabetes, which didn't receive insulin-containing medicine, served as control groups.

As seen from the figures in table 1, glucose level in the blood of animals with streptozotocine diabetes in three hours upon the injection of insulin-containing medicine reduced averagely by 65% in comparison with the diabetic animals, which didn't receive insulin-containing medicine.

Example 4: insulin-containing medicine, derived as in the example 1, was injected into adult male mice with mass 20g through probe in the volume of 0,2ml. The animals received 2,0-2,5 units of insulin in insulin-containing medicine. Glucose content in the blood was determined through glucose-oxide method. The results are provided in table 2.

From the figures provided it is vividly seen that insulin-containing medicine when injected into mice reduces glucose level in the blood averagely by 55% in comparison with animals, which didn't receive insulin-containing medicine.

Example 5: Insulin-containing medicine, derived as in the example 2 as taken 10-15 units, was injected into male rats with mass 150-180g and in 3-6 hours glucose level was determined. Rats, which didn't receive insulin-containing medicine, served as control groups. The figures are provided in table 3.

As seen from the figures in table 3 those rats, which received insulin-containing medicine in 3 and 6 hours, showed reduction in glucose level in their blood, that made 52% and 53% respectively to the initial level, at a time when glucose level in the blood of control animals within the same time spell didn't change at all.

Medicine in the process of manufacturing or in a ready form may be processed by gelatin or any other inertial compound, and prior to use may be suspended in the water. Medicine may be manufactured in the form of tablets, protected by any inertial related compound as well as applied in the form of suspension, which may be kept under the temperature +4° C for not less than 3 months.

Table 1.

Groups of animals	Quantity of animals	Glucose in blood, mM/l		% of reduction to control
		M ± m	p	
Without insulin-containing medicine (norm, 100%)	20	16,10± 0,74		
Insulin-containing medicine in accordance with the invention	20	5,62 ± 0,44	<0,01	65

Table 2.

Groups of animals	Quantity of animals	Glucose in blood, mM/l		% of reduction to norm
		average	fluctuation limits	
Without insulin-containing medicine (norm, 100%)	10	14,20	13,80 ± 4,22	
Insulin-containing medicine in accordance with the invention	10	6,21	5,74 ± 1,76	57

Table 3.

Groups of animals	Quantity of animals	Glucose in blood, mM/l				
		initial	in 3 hours	% of reduction	in 6 hours	% of reduction
Insulin-containing medicine of peroral use	10	15,5± 2,6<	7,5 ± 2,4 p<0,01	52	7,24 ± 1,78 p<0,01	53
Control without insulin-containing medicine	10	15,6 ± 2,5	14,1 ± 2,5 p>0,5	45	14,1 ± 2,6 p>0,5	2,1

Table 4.

Duration of storage in years	Glucose content in blood** mM/l		% of reduction
	initial	in 3 hours	
0,01	15,5 ± 1,0	6,2 ± 0,5	60
0,5	14,8 ± 0,9	5,6 ± 0,4	62
1	16,1 ± 0,7	6,7 ± 0,6	58
2	15,0 ± 0,9	6,1 ± 0,5	59
4	16,5 ± 0,7	6,7 ± 0,7	61
5	14,9 ± 0,5	5,9 ± 0,6	6,0

* - dried in a lyophilized way

** - injection of medicine into rats with streptozotocine diabetes in peroral way

TECHNICAL APPLICABILITY

Insulin-containing medicine for peroral use may be used not only for treatment of diabetes but for other types of pathology as well, followed by hyperglycemia (extensive surgical wounds, thermal injuries, septic condition, haemorrhoidal shock, anesthesia) as well as during pathological states characterized with the increased albumen decomposition and its decreased synthesis (various stages of burn disease, nephropathies etc.).

CLAIMS

1. Insulin-containing medicine for peroral use containing insulin and auxiliary substance, characterized in the fact that it contains insulin immobilized on erythrocytes of fresh mammal blood in the presence of stitching agent in proportion, in mass %:

insulin	5-10
erythrocytes excreted from fresh mammal blood	100

and represents a lyophilized form with the content 1250-2000E of insulin on 1g of dry mass.

2. Medicine on item 1, distinguished for the fact that it contains gelatin as an auxiliary substance.

3. Medicine on any of the items 1 or 2, characterized in the fact that the content of auxiliary substance makes 1-2,5 mass%.

4. Medicine on any of the items 1-3, characterized in the fact that erythrocytes excreted from fresh pig, livestock or horse blood can be used as erythrocytes.

5. Medicine on any of the items 1-3, characterized in the fact that it contains erythrocytes excreted from fresh human blood.

6. Medicine on any of the items 1-5, characterized in the fact that it contains glutarite dialdehyde.

7. The method for derivation of insulin-containing medicine for peroral use, including the excretion of erythrocytes, from fresh mammal blood, their incubation with insulin in the presence of stitching agent, washing of immobilized insulin with physiological solution, adding of stabilizer and lyophilization, distinguished for the fact that the incubation of erythrocytes with insulin is carried out in proportion insulin: erythrocytes

under the temperature 4-8°C within 4-6 hours, along with this, in the process of excretion of erythrocytes the blood is influenced by centrifugal forces with the size 350-1100*g within 15-30 minutes, and during insulin incubation with erythrocytes pendular rocking of composition with frequency 0,1-0,5Hz is performed, moreover, washing of immobilized insulin is carried out in several cycles with centrifugal forces being in effect during each of the cycles with the size 350-1100*g within 0,5-10,0 minutes.

8. Method on item 7, characterized in the fact that gelatin is used as a stabilizer.

9. Method on item 8, characterized in the fact that gelatin in the quantity 1-2,5 mass% is used as a stabilizer.

10. Method on any of the items 7-9, characterized in the fact that erythrocytes excreted from fresh pig, livestock or horse blood are used as erythrocytes.

11. Method on any of the items 7-9, characterized in the fact that it contains erythrocytes excreted from fresh human blood.

12. Method on any of the items 7-11, characterized in the fact that it contains glutarite dialdehyde as a stitching agent.

ABSTRACT

The invention refers to medical science and deals with insulin-containing medicine for peroral use and its derivation method.

Insulin-containing medicine for peroral use containing insulin and auxiliary substance, wherein it contains insulin immobilized on erythrocytes of fresh mammal blood in the presence of stitching agent in proportion, in mass %:

insulin	5-10
erythrocytes excreted from fresh mammal blood	100

and represents a lyophilized form with the content 1250-2000E of insulin on 1g of dry mass.

DECLARATION AND POWER OF ATTORNEY U.S.A.

FOR ATTORNEYS' USE ONLY

ATTORNEYS' DOCKET NO.

ALL PATENTS, INCLUDING DESIGN
FOR APPLICATION BASED ON PCT; PARIS CONVENTION;
NON PRIORITY; OR PROVISIONAL APPLICATIONS

As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below), or an original, first and joint inventor (if plural inventors are named below at 201-203, or on additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled:

101 / 102

INSULIN-CONTAINING MEDICAMENT FOR PERORAL APPLICATION AND METHOD FOR THE PRODUCTION THEREOF

which is described and claimed in: ☒ PCT International Application No. PCT/RU99/00163 filed 01 December 1999

☒ the attached specification ☐ the specification in application Serial No. _____ filed _____

(if applicable) and amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.
I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

103 / 104

Prior Foreign Application(s) (Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed Yes	No
99124800	RUSSIA	30 November 1999	☒	☐
			☐	☐
			☐	☐

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application No. _____ Filing Date _____ Application No. _____ Filing Date _____

105

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status: patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys (Registration No.) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith. HARVEY B. JACOBSON, JR. (20,851); D. DOUGLAS PRICE (24,514); JOHN CLARKE HOLMAN (22,769); MARVIN R. STERN (20,640); MICHAEL R. SLOBASKY (26,421); JONATHAN L. SCHERER (29, 851); IRWIN M. AISENBERG (19,007); WILLIAM E. PLAYER (31,409)

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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201*	SIGNATURE OF INVENTOR 202*	SIGNATURE OF INVENTOR 203*
DATE 26.01.2001	DATE	DATE

*. Additional inventors are named on separately numbered sheets attached hereto.